REMARKS

I. Status of Claims

Claims 1-8, 26-29, 31, and 32 are pending in this application. Claims 9-25 and 30 were cancelled.

In the present Amendment, claims 1-3, 5, 8, 26, 27, 29, 31, and 32 have been amended to appropriately claim the present invention. Support for the amendments can be found in the originally-filed specification. Specifically, the compounds that are added in claim 29 are the compound in Example 17 (disclosed on page 53 of the specification), as well as compound 148 (page 94), compound 166 (page 97), compound 184 (page 100), and compounds 199, 200, and 202 (page 102). Therefore, no new matter has been raised by the amendments.

II. Rejection under 35 U.S.C. § 102

The Examiner rejects claims 1-6, 26, and 27 under 35 U.S.C. § 102(a) as being anticipated by WO 2002022587 A1 to Nagato et al. ("Nagato"). Office Action, page 2. Specifically, the Examiner states that "the base compound with RN 404933-57-9 was found to be an index error" by Chemical Abstract Services. *Id.* at page 3. However, the Examiner alleges that the compound, 2,3-dihydro-N-[2-(4-morpholinyl)ethyl]-3-oxo-6-phenyl-4-pyridazinecarboxamide monohydrochloride, disclosed in Nagato (i.e., an intermediate disclosed in Example 12 of the English equivalent of Nagato, U.S. Patent Application Publication No. 2003/0225081, at page 29, first column, lines 7-8) anticipates the rejected claims. *Id.* at pages 2-4.

Applicants respectfully disagree with the Examiner, because the compound, 2,3-dihydro-N-[2-(4-morpholinyl)ethyl]-3-oxo-6-phenyl-4-pyridazinecarboxamide

monohydrochloride, does not fall into the scope of the rejected claims as currently amended. Therefore, this rejection is improper in view of the current amendments. Accordingly, Applicants respectfully request this rejection be withdrawn.

III. Rejection under 35 U.S.C. § 103

The Examiner also rejects claims 1-7, 26, and 27 under 35 U.S.C. § 103(a) as being unpatentable over WO 99/44995 to Yoshizaki et al. ("Yoshizaki") for the reasons of record. Office Action, pages 4-5. In addition, the Examiner alleges that "this is a homolog issue that is commonly raised in obviousness rejections." *Id.* at pages 6-7 (citing M.P.E.P. § 2144.08.II.A.4(c)). Applicants respectfully disagree with the Examiner for the reasons of the record and the following additional reasons.

In the recently decided *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.* case (a copy of which is enclosed for the Examiner's convenience), the Federal Circuit explained that a *prima facie* case of obviousness regarding a claimed compound that is structurally similar to a prior art compound is only made out when the prior art gives reason or motivation to make the claimed compound. 83 USPQ2d 1169, 1174 (Fed. Cir. 2007). The court also explained that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." *Id.* The court noted that while a "known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties'", it still remained necessary "in cases involving new chemical compounds ... to identify *some reason that would have led a chemist to modify a known compound in a*

particular manner to establish a prima facie case of obviousness of a new claimed compound." *Id.* (emphasis added). The Federal Circuit went on to confirm that the test outlined hereinabove for establishing a *prima facie* case of obviousness of a claimed compound that is structurally similar to a prior art compound is consistent with the legal principles set forth in the recently decided Supreme Court case, *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). *Id.*

The facts of *Takeda* resemble those in the present case. In *Takeda*, the obviousness challenge was predicated on first selecting a specific compound from the prior art, and then modifying the specifically selected prior art compound in the manner needed to arrive at the compound in dispute. *Id.* at 1174-75. The only difference between the prior art compound and the compound at issue in *Takeda* was a methyl group attached to the 6-position of the pyridinyl of the prior art compound versus an ethyl group attached to the 5-position of the pyridinyl of the compound in dispute. *Id.* at 1171-72. The Federal Circuit affirmed the district court's finding that there was no motivation in the prior art to choose the specifically selected 6-methylpyridinyl prior art compound as the lead compound. *Id.* at 1173.

Similarly, here, the Examiner has failed to point to any evidence of reason or motivation in the prior art to choose the particular compound relied upon by the Examiner as the lead compound from the myriad of compounds disclosed in Yoshizaki, especially given the fact that that compound is an intermediate.

Further, even under *KSR*, the Examiner needs to point to some reason why one of ordinary skill in the art would modify a known compound in a particular manner to

establish a *prima facie* case of obviousness of a new claimed compound. *Id.* at 1174. Because the Examiner has failed to do so, this rejection is improper.

In addition, "[h]omology should not be automatically equated with *prima facie* obviousness." M.P.E.P. § 2144.09 II, page 2100-160, Rev. 6, Sept. 2007. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *Id.* at § 2144.09 I, page 2100-159 (quoting *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979)). The Examiner has, however, failed to point to any evidence that the intermediate compound disclosed in Yoshizaki has similar properties as the claimed compounds. Therefore, this rejection is improper.

Accordingly, Applicants respectfully request this rejection be withdrawn.

IV. Claim Objections

The Examiner objects to claims 26, 27, 31, and 32, because of the term "pharmaceutical preparation" that is used therein. Office Action, page 7. The Examiner suggested to amend "pharmaceutical preparation" to "pharmaceutical composition." *Id.*

Solely to advance the prosecution of the present application, Applicants have amended claims 26, 27, 31, and 32 according to the Examiner's suggestions. Therefore, Applicants respectfully request this objection be withdrawn.

V. Allowable Subject Matter

Applicants acknowledge, with appreciation, the indication of allowable subject matter in claims 8, 28, and 29, and note that claims 8 and 28 are objected to as based on rejected parent claims. *See id.* Despite the indication that claims 8 and 28 would

be allowed if rewritten in independent form, Applicants have decided to keep these claims in dependent form, as Applicants believe that all of the rejections should be withdrawn as discussed above. Accordingly, Applicants respectfully request this objection be withdrawn and all of the pending claims be allowed.

VI. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

If the Examiner believes a telephone conference would be useful in resolving any outstanding issues, the Examiner is invited to call the Applicants' undersigned representative at (202) 408-4218.

If there is any fee due in connection with the filing of this response, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 14, 2008

By: _____
Ningling Wang
Reg. No. 52,412

Attachment:

A copy of the decision in *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007).

83 USPQ2d 1169

Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.

U.S. Court of Appeals
Federal Circuit

No. 06-1329

Decided June 28, 2007

492 F3d 1350

Headnotes

PATENTS

[1] Patentability/Validity — Obviousness — Relevant prior art — In general (▶115.0903.01)

Prima facie case of obviousness for claimed chemical compound requires showing of structural similarity between prior art compound and claimed compound, as well as showing that prior art would have suggested making specific molecular changes necessary to achieve claimed invention; this test is consistent with legal principles prohibiting rigid application of "teaching, suggestion, or motivation" test in obviousness inquiry, since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish prima facie obviousness of new compound.

[2] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (▶115.0903.03)

Infringement defendants failed to show that person of ordinary skill in art would have selected

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prior-art "compound b" thiazolidinedione as "lead compound," or compound that would be most promising to modify, in formulating claimed TZD derivatives used as antidiabetic agents, since plaintiffs' prior patent, which disclosed test results for nine specific compounds including compound b, does not suggest to one of skill in art that those nine compounds, out of hundreds of millions of compounds covered by application, were best-performing compounds as antidiabetics, since prior art article that examined antidiabetic effects of 101 TZD compounds, including compound b, did not identify compound b as one of most effective compounds, and instead singled out that compound as causing "considerable increases in body weight and brown fat weight," since statement in prior patent characterizing compound b as "especially important" was essentially negated by disclosure of prior art article, which taught away from compound b, and since admissions by defendants' witnesses support conclusion that compound b would not have been suitable compound for "lead compound" status.

[3] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (▶115.0903.03)

Claimed thiazolidinedione derivatives used as antidiabetic agents cannot be found obvious over closest prior art compound, identified as "compound b," under "obvious to try" standard, since that standard is applicable if prior art contains finite number of identified, predictable solutions, whereas prior art in present case, rather than identifying predictable solutions for antidiabetic treatment, disclosed broad selection of compounds, any one of which could have been selected as "lead compound" for further investigation, and since compound b exhibited negative properties that would have directed person of ordinary skill in art away from that compound; nothing in prior art provided motivation to narrow possibilities for lead compound to compound b, since evidence

supports finding that one of ordinary skill would have chosen as starting point one of more than 90 compounds in prior art that did not disclose existence of toxicity or side effects, rather than compound with identified adverse effects.

[4] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (▶115.0903.03)

Infringement defendants failed to show that prior art suggested making specific molecular modifications to closest prior art compound that are necessary to achieve claimed thiazolidinedione derivatives used as antidiabetic agents, since obtaining claimed compounds from closest prior art compound, identified as "compound b," requires steps of homologating methyl group of compound b, and moving resulting ethyl group to 5-position on pyridyl ring, since evidence supports finding that there was no reasonable expectation in art that adding methyl group to compound b would reduce or eliminate known toxicity of that compound, or that changing positions of substituent on pyridyl ring would result in beneficial changes, since any presumed expectation that compound b and claimed compounds would share similar properties due to their structural similarities is rebutted by evidence that claimed compounds exhibit unexpectedly superior properties over compound b in terms of toxicity, and since record does not support defendants' contention that patentee, during prosecution of prior patent, stated that making changes to pyridyl region of compound b would lead to "better toxicity" than prior art.

[5] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (▶115.0903.03)

Federal district court did not exclude prosecution history of prior patent from scope of prior art for invention of patent in suit after concluding that prosecution history was not accessible to public, and court therefore did not commit reversible error, since record shows that court considered prosecution history of prior patent, and even expressly considered key statement therein on which defendants relied in making their obviousness argument; thus, although district court may have incorrectly implied that prosecution histories are not accessible to public, any error committed by court in this regard was harmless.

Particular Patents

Particular patents — Chemical — Diabetes treatment

4,687,777, Meguro and Fujita, thiazolidinedione derivatives useful as antidiabetic

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agents, judgment that patent is not invalid for obviousness affirmed.

Case History and Disposition

Appeal from the U.S. District Court for the Southern District of New York, Cote, J.

Action by Takeda Chemical Industries Ltd. and Takeda Pharmaceuticals North America Inc. against Alphapharm PTY. Ltd. and Genpharm Inc. for patent infringement. Defendants appeal from decision, following bench trial, that patent in suit is not invalid for obviousness. Affirmed; Dyk, J., concurring in separate opinion.

Related decision: 71 USPQ2d 1739.

Attorneys

David G. Conlin, Barbara L. Moore, Kathleen B. Carr, and Adam P. Samansky, of Edwards Angell Palmer & Dodge, Boston, Mass.; Anthony J. Viola, of Edwards Angell Palmer & Dodge, New York, N.Y.; Mark Chao, Takeda Pharmaceuticals North America Inc., Lincolnshire, Ill., for plaintiffs-appellees.

Kevin F. Murphy, Edgar H. Haug, and Jeffrey A. Hovden, of Frommer Lawrence & Haug, New York, for defendants-appellants.

Judge

Before Lourie, Bryson, and Dyk, circuit judges.

Opinion Text

Opinion By:

Lourie, J.

Alphapharm Pty., Ltd. and Genpharm, Inc. (collectively "Alphapharm") appeal from the decision of the United States District Court for the Southern District of New York, following a bench trial, that U.S. Patent 4,687,777 was not shown to be invalid under 35 U.S.C. §103. *Takeda Chem. Indus., Ltd. v. Mylan Labs.*, 417 F.Supp.2d 341 (S.D.N.Y. 2006). Because we conclude that the district court did not err in determining that the claimed compounds would not have been obvious in light of the prior art, and hence that the patent has not been shown to be invalid, we affirm.

BACKGROUND

Diabetes is a disease that is characterized by the body's inability to regulate blood sugar. It is generally caused by inadequate levels of insulin—a hormone produced in the pancreas. Insulin allows blood sugar or glucose, which is derived from food, to enter into the body's cells and be converted into energy. There are two types of diabetes, known as Type 1 and Type 2. In Type 1 diabetes, the pancreas fails to produce insulin, and individuals suffering from this type of diabetes must regularly receive insulin from an external source. In contrast, Type 2 diabetic individuals produce insulin. However, their bodies are unable to effectively use the insulin that is produced. This is also referred to as insulin resistance. As a result, glucose is unable to enter the cells, thereby depriving the body of its main source of energy. Type 2 diabetes is the most common form of diabetes—affecting over 90% of diabetic individuals.

In the 1990s, a class of drugs known as thiazolidinediones ("TZDs") was introduced on the market as a treatment for Type 2 diabetes. Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda") first invented certain TZDs in the 1970s. Takeda's research revealed that TZDs acted as insulin sensitizers, *i.e.*, compounds that ameliorate insulin resistance. Although the function of TZDs was not completely understood, TZDs appeared to lower blood glucose levels by binding to a molecule in the nucleus of the cell known as PPAR-gamma, which activates insulin receptors and stimulates the production of glucose transporters. *Takeda*, 417 F.Supp.2d at 348-49. The transporters then travel to the cellular surface and enable glucose to enter the cell from the bloodstream. *Id.*

Takeda developed the drug ACTOS®, which is used to control blood sugar in patients who suffer from Type 2 diabetes. ACTOS® has enjoyed substantial commercial success since its launch in 1999. By 2003, it held 47% of the TZD market, and gross sales for that year exceeded $1.7 billion. *Id.* at 386. The active ingredient in ACTOS® is the TZD compound pioglitazone, a compound claimed in the patent in suit.

Takeda owns U.S. Patent 4,687,777 (the "'777 patent") entitled "Thiazolidinedione Derivatives, Useful As Antidiabetic Agents." The patent is directed to "compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." '777 patent col.1 ll.34-37. The asserted claims are claims 1, 2, and 5. Claim 1 claims a genus of compounds. Claim 5 claims pharmaceutical compositions containing that genus of compounds. Those claims read as follows:

1. A compound of the formula:

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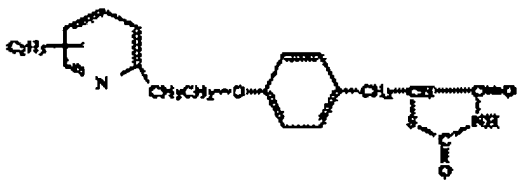
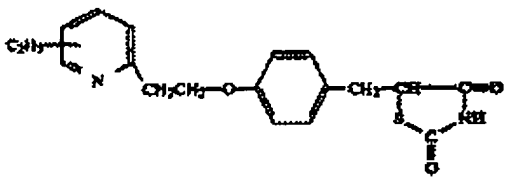


or a pharmacologically acceptable salt thereof.

5. An antidiabetic composition which consists essentially of a compound of the formula:



or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.

Id., claims 1 & 5.

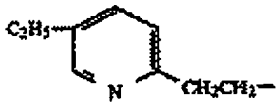
For purposes of this appeal, the critical portion of the compound structure is the left moiety of the molecule, namely, the ethyl-substituted pyridyl ring. [1] That chemical structure, which has an ethyl substituent (C2H5) pictorially drawn to the center of the pyridyl ring, indicates that the structure covers four possible compounds, *viz.*, compounds with an ethyl substituent located at the four available positions on the pyridyl ring. *Takeda*, 417 F.Supp.2d at 360. The formula includes the 3-ethyl compound, 4-ethyl compound, 5-ethyl compound (pioglitazone), and 6-ethyl compound.

[1] Pyridine is a "six-membered carbon-containing ring with one carbon replaced by a nitrogen." *Takeda*, 417 F.Supp.2d at 351.

Claim 2 of the '777 patent covers the single compound pioglitazone. That claim, which depends from claim 1, reads:

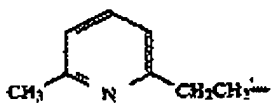
> 2. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione.

'777 patent, claim 2. Pioglitazone is referred to as the 5-ethyl compound because the ethyl substituent is attached to the 5-position on the pyridyl ring. That portion of the compound is depicted as:



Alphapharm, a generic drug manufacturer, filed an Abbreviated New Drug Application ("ANDA") pursuant to the Hatch-Waxman Act seeking U.S. Food and Drug Administration ("FDA") approval under 21 U.S.C. §355(j) et seq. to manufacture and sell a generic version of pioglitazone. Alphapharm filed a Paragraph IV certification with its ANDA pursuant to §505(j)(2)(B)(ii), asserting that the '777 patent is invalid as obvious under 35 U.S.C. §103. In response, Takeda sued Alphapharm, along with three other generic drug manufacturers who also sought FDA approval to market generic pioglitazone, alleging that the defendants have infringed or will infringe the '777 patent.

On January 17, 2006, the district court commenced a bench trial solely on the issues of validity and enforceability of the '777 patent. Alphapharm advanced its invalidity argument, asserting that the claimed compounds would have been obvious at the time of the alleged invention. Alphapharm's obviousness contention rested entirely on a prior art TZD compound that is referenced in Table 1 of the '777 patent as compound b. The left moiety of compound b consists of a pyridyl ring with a methyl (CH3) group attached to the 6-position of the ring. That portion of its chemical structure is illustrated as follows:



Alphapharm asserted that the claimed compounds would have been obvious over compound b.

The district court found that Alphapharm failed to prove by clear and convincing evidence that the asserted claims were invalid as obvious under 35 U.S.C. §103. The court first concluded that there was no motivation in the prior art to select compound b as the lead

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compound for antidiabetic research, and that the prior art taught away from its use. As such, the court concluded that Alphapharm failed to make a prima facie case of obviousness. The court continued its analysis and found that even if Alphapharm succeeded in making a prima facie showing, Takeda would

still prevail because any prima facie case of obviousness was rebutted by the unexpected results of pioglitazone's nontoxicity. The court then rendered judgment in favor of Takeda. The district court also held that the '777 patent had not been procured though inequitable conduct. That decision has been separately appealed and has been affirmed in a decision issued today.

Alphapharm timely appealed. We have jurisdiction pursuant to 28 U.S.C. §1295(a)(1).

DISCUSSION

A. Standard of Review

In this appeal, we are presented with one issue, namely, whether the asserted claims of the '777 patent would have been obvious under 35 U.S.C. §103 at the time the invention was made. An invention is not patentable, *inter alia*, "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. §103(a). Because a patent is presumed to be valid, 35 U.S.C. §282, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1238-39 [68 USPQ2d 1280] (Fed. Cir. 2003). Whether an invention would have been obvious under 35 U.S.C. §103 is a "question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 [80 USPQ2d 1001] (Fed. Cir. 2006).

B. Obviousness

Alphapharm raises three main arguments in support of its contention that the claims would have been obvious. First, Alphapharm asserts that the district court misapplied the law, particularly the law governing obviousness in the context of structurally similar chemical compounds. According to Alphapharm, the record established that compound b was the most effective antidiabetic compound in the prior art, and thus the court erred by failing to apply a presumption that one of ordinary skill in the art would have been motivated to make the claimed compounds. Alphapharm asserts that such a conclusion is mandated by our case law, including our en banc decision in *In re Dillon*, 919 F.2d 688 [16 USPQ2d 1897] (Fed. Cir. 1990). Second, Alphapharm argues that the court erred in determining the scope and content of the prior art, in particular, whether to include the prosecution history of the prior '779 patent. Lastly, Alphapharm assigns error to numerous legal and factual determinations and certain evidentiary rulings that the court made during the course of the trial.

Takeda responds that the district court correctly determined that Alphapharm failed to prove by clear and convincing evidence that the asserted claims are invalid as obvious. Takeda contends that there was overwhelming evidence presented at trial to support the court's conclusion that no motivation existed in the prior art for one of ordinary skill in the art to select compound b as a lead compound, and even if there was, that the unexpected results of pioglitazone's improved toxicity would have rebutted any prima facie showing of obviousness. Takeda further argues that all of Alphapharm's remaining challenges to the district court's legal and factual rulings are simply without merit.

We agree with Takeda that the district court did not err in concluding that the asserted claims of the '777 patent would not have been obvious. The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385] (2007). The Court stated that the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 [148 USPQ 459] (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR*, 127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18).

In a thorough and well-reasoned opinion, albeit rendered before *KSR* was decided by the Supreme Court, the district court made extensive findings of fact and conclusions of law

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as to the four *Graham* factors. Alphapharm's arguments challenge the court's determinations with respect to certain of these factors, which we now address.

1. Differences Between the Prior Art and the Claims

a. election of Compound b as Lead Compound

Alphapharm's first argument challenges the court's determination with regard to the "differences between the prior art and the claims." Alphapharm contends that the court erred as a matter of law in

holding that the ethyl-substituted TZDs were nonobvious in light of the closest prior art compound, compound b, by misapplying the law relating to obviousness of chemical compounds.

[1] We disagree. Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 [226 USPQ 870] (Fed. Cir. 1985).

We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 [34 USPQ2d 1210] (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 [21 USPQ2d 1941] (Fed. Cir. 1992); *Dillon*, 919 F.2d 688 [16 USPQ2d 1897] ; *Grabiak*, 769 F.2d 729 [226 USPQ 870]; *In re Lalu*, 747 F.2d 703 [223 USPQ 1257](Fed. Cir. 1984)).

That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*. [2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

[2] We note that the Supreme Court in its *KSR* opinion referred to the issue as whether claimed subject matter "was" or "was not" obvious. Since 35 U.S.C. §103 uses the language "would have been obvious," and the Supreme Court in *KSR* did consider the particular time at which obviousness is determined, we consider that the Court did not in *KSR* reject the standard statutory formulation of the inquiry whether the claimed subject matter "would have been obvious at the time the invention was made." 35 U.S.C. §103. Hence, we will continue to use the statutory "would have been" language.

We agree with Takeda and the district court that Alphapharm failed to make that showing here. Alphapharm argues that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound. By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity. [3]

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Upon selecting that compound for antidiabetic research, Alphapharm asserts that one of ordinary skill in the art would have made two obvious chemical changes: first, homologation, *i.e.*, replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone. Thus, Alphapharm's obviousness argument clearly depends on a preliminary finding that one of ordinary skill in the art would have selected compound b as a lead compound.

[3] The parties do not dispute that compound b was the closest prior art compound. Thus, the legal question is whether or not the claimed subject matter would have been obvious over that compound. We will, however, use Alphapharm's terminology of "lead compound" in this opinion, deciding the appeal as it has been argued.

[2] The district court found, however, that one of ordinary skill in the art would not have selected compound b as the lead compound. In reaching its determination, the court first considered Takeda's U.S. Patent 4,287,200 (the "'200 patent"), which was issued on September 1, 1981, and its prosecution history. The court found that the '200 patent "discloses hundreds of millions of TZD compounds." [4] *Takeda*, 417 F.Supp.2d at 378. The patent specifically identified fifty-four compounds, including compound b, that were synthesized according to the procedures described in the patent, but did not disclose experimental data or test results for any of those compounds. The prosecution history, however, disclosed test results for nine specific compounds, including compound b. That information was provided to the examiner in response to a rejection in order to show that the claimed compounds of the '200 patent were superior to the known compounds that were disclosed in a cited reference. The court, however, found nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties. *Id.* at 375.

[4] Three divisional applications derive from the '200 patent. Those applications matured into U.S. Patent 4,340,605, U.S. Patent 4,438,141, and U.S. Patent No. 4,444,779 (the "'779 Patent"). The '779 patent is of particular relevance in this appeal and is discussed below. *Takeda*, 417 F.Supp.2d at 378.

The court next considered an article that was published the following year in 1982 by T. Sodha et al. entitled "Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl] thiazoli- dine-2,4-dione (ADD-3878) and Its Derivatives" ("Sodha II"). The Sodha II reference disclosed data relating to hypoglycemic activity and plasma triglyceride lowering activity for 101 TZD compounds. Those compounds did not include pioglitazone, but included compound b. Significantly, Sodha II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

The court also considered Takeda's '779 patent. That patent covers a subset of compounds originally included in the '200 patent application, namely, TZD compounds "where the pyridyl or thiazolyl groups may be substituted." *Id.* at 353. The broadest claim of the '779 patent covers over one million compounds. *Id.* at 378. Compound b was specifically claimed in claim 4 of the patent. The court noted that a preliminary amendment in the prosecution history of the patent contained a statement that "the compounds in which these heterocyclic rings are substituted have become important, especially [compound b]." *Id.*

Based on the prior art as a whole, however, the court found that a person of ordinary skill in the art would not have selected compound b as a lead compound for antidiabetic treatment. Although the prosecution history of the '779 patent included the statement that characterized compound b as "especially important," the court found that any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary skill in the art would not have chosen compound b, notwithstanding the statement in the '779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 [p]atent showing that there were many promising, broad avenues for further research." *Id.* at 380.

The court found that the three compounds that the Sodha II reference identified as "most

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favorable" and "valuable for the treatment of maturity-onset diabetes," not compound b, would have served as the best "starting point for further investigation" to a person of ordinary skill in the art. *Id.* at 376. Because diabetes is a chronic disease and thus would require long term treatment, the court reasoned that researchers would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects, especially one that causes "considerable increases in body weight and brown fat weight." *Id.* at 376-77. Thus, the court determined that the prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research.

Admissions from Alphapharm witnesses further buttressed the court's conclusion. Dr. Rosenberg, head

of Alphapharm's intellectual property department, testified as a 30(b)(6) witness on behalf of Alphapharm. In discussing Sodha II, Dr. Rosenberg admitted that there was nothing in the article that would recommend that a person of ordinary skill in the art choose compound b over other compounds in the article that had the same efficacy rating. Dr. Rosenberg, acknowledging that compound b had the negative side effects of increased body weight and brown fat, also admitted that a compound with such side effects would "presumably not" be a suitable candidate compound for treatment of Type II diabetes. Alphapharm's expert, Dr. Mosberg, concurred in that view at his deposition when he admitted that a medicinal chemist would find such side effects "undesirable."

Moreover, another Alphapharm 30(b)(6) witness, Barry Spencer, testified at his deposition that in reviewing the prior art, one of ordinary skill in the art would have chosen three compounds in Sodha II as lead compounds for research, not solely compound b. In addition, Takeda's witness, Dr. Morton, testified that at the time Sodha II was published, it was known that obesity contributed to insulin resistance and Type 2 diabetes. Thus, one of ordinary skill in the art would have concluded that Sodha II taught away from pyridyl compounds because it associated adverse side effects with compound b.

We do not accept Alphapharm's assertion that *KSR*, as well as another case recently decided by this court, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 [82 USPQ2d 1321] (Fed. Cir. 2007), mandates reversal. Relying on *KSR*, Alphapharm argues that the claimed compounds would have been obvious because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." Additionally, Alphapharm argues that our holding in *Pfizer*, where we found obvious certain claims covering a particular acid-addition salt, directly supports its position.

[3] We disagree. The *KSR* Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under §103." *Id.* That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

Similarly, Alphapharm's reliance on *Pfizer* fares no better. In *Pfizer*, we held that certain claims covering the besylate salt of amlodipine would have been obvious. The prior art included a reference, referred to as the Berge reference, that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically acceptable acid addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt. *Pfizer*, 480 F.3d at 1363. Noting that our conclusion was based on the "particularized facts of this case," we found that the prior art provided "ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate." *Id.* at 1363, 1367. Here, the court found nothing in the prior art to narrow the possibilities of a lead

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compound to compound b. In contrast, the court found that one of ordinary skill in the art would have chosen one of the many compounds disclosed in Sodha II, of which there were over ninety, that "did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, rather than to choose as a starting point a compound with identified adverse effects." Thus, *Pfizer* does not control this case.

Based on the record before us, we conclude that the district court's fact-findings were not clearly erroneous and were supported by evidence in the record. Moreover, we reject the assertion that the court failed to correctly apply the law relating to prima facie obviousness of chemical compounds. Because Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound, and Alphapharm failed to prove that assertion, the court did not commit reversible error by failing to apply a presumption of motivation. We thus conclude that the court did not err in holding that Alphapharm failed to establish a prima facie case of obviousness. *See Eli Lilly & Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369 [81 USPQ2d 1324] (Fed. Cir. 2006) (affirming the district court's finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as

a lead compound).

b. Choice of the Claimed Compounds

Even if Alphapharm had established that preliminary finding, and we have concluded that it did not, the record demonstrates that Alphapharm's obviousness argument fails on a second ground. The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. *Takeda*, 417 F.Supp.2d at 380. Dr. Mosberg opined that the steps of homologation and ring-walking were "routine steps in the drug optimization process," but the court found that testimony unavailing in light of the contrary, more credible, testimony offered by Takeda's experts. *Id.* at 381. In addition, the court relied on Dr. Rosenberg's admission that a person of ordinary skill in the art would "look at a host of substituents, such as chlorides, halides and others, not just methyls" in modifying the pyridyl ring. *Id.*

[4] Pioglitazone differs from compound b in two respects, and one would have to both homologate the methyl group of compound b and move the resulting ethyl group to the 5-position on the pyridyl ring in order to obtain pioglitazone. With regard to homologation, the court found nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity. Based on the test results of the numerous compounds disclosed in Sodha II, the court concluded that "homologation had no tendency to decrease unwanted side effects" and thus researchers would have been inclined "to focus research efforts elsewhere." *Id.* at 383. Indeed, several other compounds exhibited similar or better potency than compound b, and one compound in particular, compound 99, that had no identified problems differed significantly from compound b in structure. *Id.* at 376 n.51. Moreover, Dr. Mosberg agreed with Takeda's expert, Dr. Danishefsky, that the biological activities of various substituents were "unpredictable" based on the disclosure of Sodha II. *Id.* at 384-85. The court also found nothing in the '200 and '779 patents to suggest to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success.

As for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes. Dr. Mosberg opined that the process of ring-walking was "known" to Takeda, but the court found that testimony inapt as it failed to support a reasonable expectation to one of ordinary skill in the art that performing that chemical change would cause a compound to be more efficacious or less toxic. *Id.* at 382. Moreover, Dr. Mosberg relied on the efficacy data of phenyl compounds in Sodha II, but the court found those data insufficient to show that the same effects would occur in pyridyl compounds.

Alphapharm relies on *In re Wilder*, 563 F.2d 457 [195 USPQ 426] (CCPA 1977), for the proposition that differences in a chemical compound's properties, resulting from a small

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change made to the molecule, are reasonably expected to vary by degree and thus are insufficient to rebut a prima facie case of obviousness. In *Wilder*, our predecessor court affirmed the Board's holding that a claimed compound, which was discovered to be useful as a rubber antidegradant and was also shown to be nontoxic to human skin, would have been obvious in light of its homolog and isomer that were disclosed in the prior art. The evidence showed that the homolog was similarly nontoxic to the human skin, whereas the isomer was toxic. The court held that "one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties." *Id.* at 460. While recognizing that the difference between the isomer's toxicity and the nontoxicity of the homolog and claimed compound "indicate[d] some degree of unpredictability," the court found that the appellant failed to "point out a single actual difference in properties between the claimed compound and the homologue," and thus failed to rebut the presumption. *Wilder*, 563 F.2d at 460.

We would note that since our *Wilder* decision, we have cautioned "that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other," *Grabiak*, 769 F.2d at 731. In addition to this caution, the facts of the present case differ significantly from the facts of *Wilder*. Here, the court found that pioglitazone exhibited unexpectedly superior properties over the prior art compound b. *Takeda*, 417 F.Supp.2d at 385. The court considered a report entitled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats" that was presented in February 1984 by Dr. Takeshi Fujita, then-Chief Scientist of Takeda's Biology Research Lab and co-inventor of the '777 patent. That report contained

results of preliminary toxicity studies that involved selected compounds, including pioglitazone and compound b. Compound b was shown to be "toxic to the liver, heart and erythrocytes, among other things," whereas pioglitazone was "comparatively potent" and "showed no statistically significant toxicity." *Id.* at 356-57. During the following months, Takeda performed additional toxicity studies on fifty compounds that had been already synthesized and researched by Takeda, including pioglitazone. The compounds were tested for potency and toxicity. The results were presented in another report by Fujita entitled "Pharmacological and Toxicological Studies of Ciglitazone and Its Analogues." Pioglitazone was shown to be the only compound that exhibited no toxicity, although many of the other compounds were found to be more potent. *Id.* at 358.

Thus, the court found that there was no reasonable expectation that pioglitazone would possess the desirable property of nontoxicity, particularly in light of the toxicity of compound b. The court's characterization of pioglitazone's unexpected results is not clearly erroneous. As such, *Wilder* does not aid Alphapharm because, unlike the homolog and claimed compound in *Wilder* that shared similar properties, pioglitazone was shown to differ significantly from compound b, of which it was not a homolog, in terms of toxicity. Consequently, Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties.

Alphapharm also points to a statement Takeda made during the prosecution of the '779 patent as evidence that there was a reasonable expectation that making changes to the pyridyl region of compound b would lead to "better toxicity than the prior art." During prosecution of the '779 patent, in response to an enablement rejection, Takeda stated that "there should be no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." That statement, however, indicates only that changes to the left moiety of a lead compound would create compounds with the same properties as the compounds of the prior art; it does not represent that lower toxicity would result. And even if the statement did so represent, it does not refer to any specific substituent at any specific position of TZD's left moiety as particularly promising. As the court correctly noted, the compounds disclosed in the '779 patent included a variety of substituents, including lower alkyls, halogens, and hydroxyl groups, attached to a pyridyl or thiazolyl group. As discussed *supra*, the district court found that the claims encompassed over one million compounds. Thus, we disagree with Alphapharm that that statement provided a reasonable expectation to one of ordinary skill in the art that performing the specific

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steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-position of the ring, would have provided a broad safety margin, particularly in light of the district court's substantiated findings to the contrary.

We thus conclude that Alphapharm's challenges fail to identify grounds for reversible error. The court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial. We do not see any error in the district court's determination that one of ordinary skill in the art would not have been prompted to modify compound b, using the steps of homologation and ring-walking, to synthesize the claimed compounds. Because the court's conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

The court properly concluded that Alphapharm did not make out a prima facie case of obviousness because Alphapharm failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds.

In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness. [5]

[5] The concurrence, while agreeing that the question of the "overbreadth" of claims 1 and 5 has been waived, states further that the 6-ethyl compound, which is within the scope of claims 1 and 5, has not been shown to possess unexpected results sufficient to overcome a prima facie case of obviousness, and hence claims 1 and 5 are likely invalid as obvious. Since waiver is sufficient to answer the point being raised, no further comment need be made concerning its substance.

2. Scope and Content of the Prior Art

Alphapharm also assigns error to the district court's determination regarding the scope and content of

the prior art. Alphapharm asserts that the court excluded the prosecution history of the '779 patent from the scope of the prior art after wrongly concluding that it was not accessible to the public. Takeda responds that the court clearly considered the '779 patent prosecution history, which was admitted into evidence on the first day of testimony. Takeda urges that the court's consideration of the prosecution history is apparent based on its extensive analysis of the '779 patent and the file history that appears in the court's opinion.

[5] We agree with Takeda that the district court did not err in its consideration of the scope of the prior art. As discussed above, the court considered the prosecution history, and even expressly considered one of the key statements in the prosecution history upon which Alphapharm relies in support of its position that compound b would have been chosen as the lead compound. *Takeda*, 417 F.Supp.2d at 378. In considering the prosecution history of the '779 patent, the court noted that Takeda filed a preliminary amendment on March 15, 1983, in which its prosecuting attorney stated that "the compounds in which these heterocyclic rings are substituted have become important, especially [the 6-methyl compound]." *Id.* The court rejected Alphapharm's assertion that that statement supported the conclusion that compound b would have been selected as a lead compound. Rather, the court found that viewing the prior art as a whole, the prior art showed "that Takeda was actively conducting research in many directions, and had not narrowed its focus to compound b." *Id.* at 379. Thus, while the district court may have incorrectly implied that prosecution histories are not accessible to the public, *see id.* at n.59, *see also Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955 (Fed. Cir. 1986) ("[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art"), the court nonetheless considered the prosecution history of the '779 patent in its obviousness analysis and accorded proper weight to the statements contained therein. Thus, any error committed by the court in this regard was harmless error.

We have considered Alphapharm's remaining arguments and find none that warrant reversal of the district court's decision.

CONCLUSION

We affirm the district court's determination that claims 1, 2, and 5 of the '777 patent have not been shown to have been obvious and hence invalid.

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AFFIRMED

Concurring Opinion Text

Concurrence By:

Dyk, J., concurring.

I join the opinion of the court insofar as it upholds the district court judgment based on a determination that a claim to pioglitazone (the 5-ethyl compound) would be non-obvious over the prior art. The problem is that only one of the three claims involved here—claim 2—is limited to pioglitazone. In my view, the breadth of the other two claims, claims 1 and 5 of U.S. Patent No. 4,867,777 ("'777 patent")—which are also referenced in the judgment—renders them likely invalid.

All of the compounds claimed in claims 1, 2 and 5 were included in generic claims in the prior art U.S. Patent No. 4,287,200 ("'200 patent"). Unfortunately our law concerning when a species is patentable over a genus claimed in the prior art is less than clear. It is, of course, well established that a claim to a genus does not necessarily render invalid a later claim to a species within that genus. *See Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 [67 USPQ2d 1161] (Fed. Cir. 2003). In my view a species should be patentable over a genus claimed in the prior art only if unexpected results have been established. Our case law recognizes the vital importance of a finding of unexpected results, both in this context and in the closely related context where a prior art patent discloses a numerical range and the patentee seeks to claim a subset of that range. *See Application of Petering*, 301 F.2d 676, 683 [133 USPQ 275] (C.C.P.A. 1962) (species found patentable when genus claimed in prior art because unexpected properties of the species were shown); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 [82 USPQ2d 1321] (Fed. Cir. 2007) (relying on lack of unexpected results in determining that species claim was obvious in view of prior art genus claim); *In re Woodruff*, 919 F.2d 1575, 1578 [16 USPQ2d 1934] (Fed. Cir. 1990) (when applicant claims a subset of a range disclosed in a prior art patent, the applicant must generally show that "the claimed range achieves unexpected results relative to the prior art range.").

While the 5-ethyl compound (pioglitazone) is within the scope of the '200 patent, there is clear evidence, as the majority correctly finds, of unexpected results regarding that compound, and therefore its validity is not in question on this ground. However, at oral argument the patentee admitted that the prior art '200 patent also generically covers the 6-ethyl compound, which is within the scope of claims 1 and 5 of the '777 patent, and admitted that there is no evidence of unexpected results for the 6-ethyl compound. Under such circumstances, I believe that the 6-ethyl is likely obvious, and consequently claims 1 and 5 are likely invalid for obviousness. However, the argument as to the overbreadth of claims 1 and 5 has been waived, because it was not raised in the opening brief. In any event, as a practical matter, the judgment finding that the appellants' filing of the ANDA for pioglitazone is an infringement and barring the making of pioglitazone is supported by the finding that claim 2 standing alone is not invalid and is infringed.

- End of Case -

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